

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-436**

**CLINICAL PHARMACOLOGY and  
BIOPHARMACEUTICS REVIEW(S)**

DEC 19 2001

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

Submission Dates: 10/31/01

NDA: 21-436  
Name of Drug: Abilitat?  
Aripiprazole (BMS-337039, OPC-14597)  
Strength: 10, 15, and 30 mg Tablets  
Indication of Drug: Schizophrenia  
Type of Submission: New NDA (NME)  
Sponsor: Otsuka, Chiyoda-ku Tokyo, Japan/BMS, Mayaguez, Puerto Rico  
Reviewer: Hong Zhao, Ph.D.

**Introduction**

The Otsuka Pharmaceutical Company (OPC) submitted this Original New Drug Application for aripiprazole tablets, a new atypical antipsychotic for the treatment of schizophrenia. The chemical name for aripiprazole is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydro-2(1H)-quinolinone. Aripiprazole was studied under IND            which was originally submitted to the Agency on June 10, 1993. Aripiprazole was developed under a collaborative agreement with Bristol-Myers Squibb Company (BMS). This agreement extends to the successful approval and commercialization of the product in the US. As a result, BMS is authorized to act on behalf of OPC in the negotiation of this NDA with the Agency.

According to the sponsor, this NDA contains information from over 4500 patients exposed to aripiprazole. The aripiprazole clinical program for schizophrenia consisted of 5 short-term Phase II/III studies, 4 long-term studies and 4 special studies. The sponsors claim that all of the short-term studies met the FDA-defined criteria for adequate and well-controlled studies. Three are considered pivotal for efficacy analyses and two are supportive. Data derived from these studies establish the robust efficacy and overall safety of aripiprazole for the treatment of patients suffering from schizophrenia.

**Clinical Pharmacology Section of the NDA**

The aripiprazole clinical pharmacology program comprised 34 clinical pharmacology studies:

- 24 studies conducted in healthy subjects, including 3 safety/pharmacokinetic studies, 1 pharmacodynamic study involving positron emission tomography, 3 drug disposition studies, 1 food interaction study, 9 drug interaction studies, 6 bioavailability or bioequivalence studies and 1 age/gender study.
- 6 studies in patients with schizophrenia or schizoaffective disorder, including 2 safety/pharmacokinetic studies, 1 population pharmacokinetic analysis, and 3 drug interaction studies.
- 4 safety/pharmacokinetic studies in patients with hepatic impairment, patients with renal impairment, elderly subjects with dementia, and children/adolescents with conduct disorder.

In addition, near 20 metabolic study reports and 6 protein binding study reports are included in Nonclinical Pharmacology and Toxicology section of the submission. Dissolution method development and data are provided in Chemistry section of the submission.

### **Formulation Support**

Dosage strengths of 2-, 5-, 10-, 15-, 20-, and 30-mg are proposed for registration. The sponsors claim that there are minor changes in formulation composition and no significant differences in dissolution between the tablets used in clinical pharmacology and Phase II/III studies versus those intended for marketing (trade). Therefore, there is no need to demonstrate bioequivalence between the clinical and proposed trade tablet forms. The bioequivalence study was conducted between 3x5 mg trade tablets and 1x15 mg tablet in healthy subjects, with AUC met the BE criteria but  $C_{max}$  with lower boundary of the 90% CI (0.75). The sponsors claim that these results support the dose strength equivalence of the proposed trade formulations.

In this NDA submission, the sponsors state the key agreement reached with FDA concerning the drug product (CMC Pre-NDA Meeting, June 22, 2001): Aripiprazole 20- and 30-mg tablets can be included in the NDA with only Certificates of Analysis in the initial filing. A bioequivalence study is required for the 30-mg tablet.

### **Comments**

The Item 6 (Human PK) of this NDA is not well compiled. The deficiencies are listed below:

- In the NDA, dosage strengths of 2-, 5-, 10, 15-, 20- and 30-mg are proposed for registration, while in the proposed label, only 10-, 15- and 30-mg strengths are available. The sponsor is requested to clarify this issue.
- Studies that require OCPB review are not included in the Item 6 (Human PK) such as in vitro metabolic studies, protein binding studies, dissolution method development and dissolution data reports.
- The Human PK part of Application Summary is only descriptive (such as "no meaningful difference, not significant different, no clinical important difference) with no PK data and PK plots presented.
- BE study reports only listed geometric means but not arithmetic means. The reviewer has to dig them out from statistical analysis printout.
- For multiple dose study there are no c-t profile plots, no  $C_{min}$  data reported in the reports. In the study synopsis only  $C_{max}$ ,  $T_{max}$  and  $T_{1/2}$  are reported, the important systemic exposure data (AUC) is missing.

- It's not clear when the sponsor will submit the ongoing drug-drug interaction study (Study 138022, with carbamazepine). Also, when dose equivalence study and food effect study for 30 mg strength will be submitted.
- Report for Population PK study is submitted with no study protocols (2 Phase II and 3 Phase III studies), study conduct and results and appendices (detail data).

Upon the request from OCPB, the sponsor have submitted the following paper volumes that are compiled in Chemistry or Preclinical sections for OCPB review: Vol. 1.4-1.5 (Dissolution method and Dissolution data), and Vol. 1.30-1.36 (Protein Binding Studies, Metabolic Studies).

**Recommendations**

On the face, this NDA is fileable from OCPB perspective provided that the following missing information is submitted immediately:

- (1) The sponsor is requested to clarify which dosage strengths do they propose to market.
- (2) The sponsor is requested to clarify when they will submit the full report for the ongoing drug-drug interaction study (Study 138022, with carbamazepine). Also, when dose equivalence study and food effect study for 30 mg strength will be submitted. All these studies should be submitted no later than 120 days following the NDA submission date (October 31, 2001).
- (3) Report for Population PK study is submitted with no study protocols (2 Phase II and 3 Phase III studies), study conduct and study results and appendices (detail data). The sponsor is requested to provide such information for review.

An additional desk copy for this study (Item 6 vol. 84, Study 31-00-233 report, Population Pharmacokinetic /Pharmacodynamic Analysis of Aripiprazole) and the electronic appendices for this study should be submitted immediately.

**Outcomes of 45-Day Filing Meeting on December 18, 2001**

On the face, this NDA is fileable provided all remaining studies should be submitted within 4 months following the NDA submission date.

**Please convey the above Comments and Recommendations to the sponsor.**

Hong Zhao, Ph.D.           |S|           12/19/01

RD/FT Initialed by Raman Baweja, Ph.D.           |S|           12/19/01.

cc: NDA 21-436 Aripiprazole (BMS-337039, OPC14597), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

## Appendix

### Reports for Bioavailability and Bioequivalence Studies

**Study 96203** (Vol. 6): Single Dose Evaluation of the Safety and Relative Bioavailability OF OPC-14597 Solution, Capsule, and Tablet in Normal Subjects (920011387 1.0)

**Study 138016** (Vol. 11-12): Open-Label, Randomized, Three-way Crossover Study of the Absolute Bioavailability of Aripiprazole 5 mg Commercial Tablet and Aripiprazole 5 mg IM Injection with Reference to 2 mg IV Infusion in Healthy Subjects (930000380 1.0)

**Study 138018** (Vol. 13-15): The Effect of a High Fat Meal and Intrasubject Variability on the Pharmacokinetics of Aripiprazole in Healthy Subjects (930000278 1.0)

**Study 138015** (Vol. 16): Study of the Effects of Aripiprazole Monohydrated Content on the Bioavailability of Aripiprazole in Healthy Subjects (920008950 3.0)

**Study 138034** (Vol. 16-20): The Effect of Aripiprazole Monohydrate Content on the Bioavailability of Aripiprazole in Healthy Subjects (920008950 4.0)

**Study 138035** (Vol. 21-23): Bioequivalence of Aripiprazole in healthy Subjects when Administered as a 15 mg Commercial Tablet as Compared with 3x5 mg Commercial Tablet (930000233 2.0)

**Study 138054** (Vol. 24): Bioequivalence of Aripiprazole in healthy Subjects when Administered as a 15 mg Commercial Tablet as Compared with a 15 mg Clinical Trial Tablet (930000385 2.0)

### Human Pharmacokinetic (PK) Study Reports

**Study 96201** (Vol. 25-29): A Study of the Absorption, Distribution, Metabolism and Excretion following Oral Administration of <sup>14</sup>C-OPC-14597 in Healthy Volunteers (920011356 1.0)

**Study 138028** (Vol. 30-31): Disposition of Dual Labeled (<sup>14</sup>C)-Aripiprazole in Healthy Male Subjects following Single Oral Administration (930000373 1.0)

**Study 138061** (Vol. 32-34): Assessment of the Biliary Excretion of DM-1454, DM-1458, and Dehydro-DM-1458 during Multiple Dose Administration of Aripiprazole to healthy Subjects (930000381 1.0)

**Study 93201** (Vol. 35-39): Multiple Ascending Dose Tolerability and Pharmacokinetic Study of OPC-14597 in Healthy Young Male Volunteers (920002236 5.0)

**Study 93204** (Vol. 40-43): Multiple Dose Tolerability and Pharmacokinetic Study of Titrated Doses of OPC-14597 in Healthy Male Volunteers of Study 31-93-204 (920002653 2.)

**Study 98202** (Vol. 44): A Pilot Study to Determine the Tolerability of Aripiprazole Doses Higher Than 30 mg Administered Orally in Patients with a Diagnosis of Schizophrenia or Schizoaffective Disorder (930000641 1.0)

**Study 99224** (Vol. 45-48): A Pilot Study to Determine the Tolerability of Aripiprazole Doses Higher than 30 mg Administered Orally in Adult Patients with a Diagnosis of Schizophrenia or Schizoaffective Disorder (930000562 1.0)

**Study 98201** (Vol.49-52): An Open-Label Study of the Effects of Diurnal Variation on the Pharmacokinetic Disposition of a Single Dose of OPC-14597 in Healthy Volunteers (920011396 1.0)

**Study 00225** (Vol. 53-59): An Open-Label Study of the Effects of Age and Gender on Single Dose Aripiprazole Pharmacokinetics in Healthy Subjects (930000264 1.0)

**Study 98203** (Vol. 60): An Open-Label, Pilot Study of the Safety and Tolerability of Aripiprazole Administered Orally in Elderly Demented Patients with Psychosis and Behavioral Disturbances (930000478 1.0)

**Study 138014** (Vol. 61-62): Tolerability, Pharmacokinetics and Pharmacodynamics of Aripiprazole during Oral Administration in Children and Adolescents with Conduct Disorder (930000382 1.0)

**Study 98205** (Vol. 63-66): A Phase I Single-Dose Evaluation of the Pharmacokinetics of Aripiprazole in Normal and Hepatically –Impaired Subjects (930000294 2.0)

**Study 98208** (Vol. 67-68): An Open-Label Study of the Pharmacokinetics of a Single Oral Dose of Aripiprazole in Normal, Healthy Subjects and Subjects with Severe Renal Impairment (930000387 1.0)

**Study 98206** (Vol. 69-79): A Double-Blind, Placebo-Controlled Study of the Effects of Orally Administered Ketoconazole on Aripiprazole (OPC-14597) Pharmacokinetics in Healthy Adult Male and Female Subjects (920011707 2.0)

**Study 98207** (Vol. 80-83): An Open-Label Study of Aripiprazole (OPC-14597) Pharmacokinetics in Healthy Adults with Poor and Extensive Metabolizer Genotype for Cytochrome P450 2D6, and the Effect of Co-administered Quinidine on Aripiprazole Pharmacokinetics (920011708 1.0)

**Study 00233** (Vol. 84): Population Pharmacokinetic Pharmacodynamic Analysis of Aripiprazole (920011833 1.0)

**Study 97205** (Vol. 85-90): Influence of Multiple Dose Administration of OPC-14597 on the Metabolism of Dextromethorphan (920011386 1.0)

**Study 00231** (Vol. 91-94): An Open-Label Study of the Influence of Co-administered Aripiprazole Oral Tablets (OPC-14597) on Dextromethorphan Oral Solution Metabolism via Cytochrome P450 2D6 in Healthy Volunteers (930000379 4.0)

**Study 00226** (Vol. 95-97): An Open-Label, Two-Period, Randomized, Crossover Study of the Effect of Increased Gastric pH by Concomitant Famotidine Administration on Aripiprazole Pharmacokinetics (930000386 1.0)

**Study 00227** (Vol. 98-100): A Single Dose, Historic-Control, Pharmacokinetic Study of orally Administered Aripiprazole (OPC-14597) in Healthy Volunteers also Receiving Activated Charcoal (930000377 1.0)

**Study 00232** (Vol. 101-104): An Open-Label Study of the Influence of Co-administered Aripiprazole Oral Tablets (OPC-14597) on Omeprazole Oral Capsule Pharmacokinetics in Healthy Volunteers (930000376 1.0)

**Study 138043** (Vol. 105-107): Effect of Concomitant Administration of Aripiprazole on the Pharmacokinetics and Pharmacodynamics of Warfarin in Healthy Male Subjects (930000258 2.0)

**Study 138022** (Vol. 108): Safety, Tolerability and Pharmacokinetics of Aripiprazole and Carbamazepine Coadministration in Patients with Schizophrenia or Schizoaffective Disorder (930000384 1.0)

**Study 138021** (Vol. 109): Safety, Tolerability and Pharmacokinetics of Aripiprazole and Lithium Coadministration in Patients with Schizophrenia or Schizoaffective Disorder (930000374 2.0)

**Study 138023** (Vol. 110): Safety, Tolerability and Pharmacokinetics of Aripiprazole and Divalproex Sodium Coadministration in Patients with Schizophrenia or Schizoaffective Disorder (930000375 1.0)

#### **Human Pharmacodynamics (PD) Study Reports**

**Study 94201** (Vol. 111-113): Interaction of OPC-14597 (30 mg/day) with Brain D2 Receptors: A Positron Emission Tomography (PET) Scan Study in Healthy Young Male Volunteers (920004456 1.0)

**Study 00239** (Vol. 114-118): A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Sequential Crossover Study of Potential Pharmacodynamic Interactions between Orally Co-administered Aripiprazole (OPC-14597) and Ethanol in Healthy Volunteers (930000378 2.0)

**Study 138030** (Vol. 119): The safety and Tolerability of Aripiprazole in the Long-Term Treatment of Schizophrenia and Schizoaffective Disorder: An Open-Label, Multi-Center Flexible Dose Trial (930000383 1.0)

**Total 34 Studies**

**Metabolic Studies**

Vol.1.32 (Pharm-Tox Vol. 20):

A Study of the Absorption, Distribution, metabolism and Excretion following Oral Administration of <sup>14</sup>C-OPC-14597 in Healthy Volunteers (Study 31-96-201) (BMS Document Control number 920011356 1.0)

The Pharmacokinetics and Metabolism of Dual Label [<sup>14</sup>C]-Aripiprazole in healthy Male Subjects (Study CN138-028) (930000373 1.0)

Vol.1.33 (Pharm-Tox Vol. 21):

Biotransformation of Dual Label [<sup>14</sup>C]-Aripiprazole in Humans after Oral Administration (930000409.4.0)

**Report-011139:** Investigation and Determination of OPC-14597 Metabolites in Human Plasma (920001395 1.1)

**Report-008556:** Identification of OPC-14597±Metabolites in Humans and Rats (2) (920001376 1.1)

Assessment of the Biliary Excretion of DM-1454, CM-1458 and DM-1460 during Multiple Dose Administration of Aripiprazole in Healthy Subjects (Study CN138-061) (930000381 1.0)

Comparative profiles of Selected Conjugated Metabolites in Bile and Plasma of Mice, Rats, Monkeys, and Humans after Daily Oral Administration of Aripiprazole (930000451 1.0)

Vol.1.35 (Pharm-Tox Vol. 23):

Determination of the Metabolite Formation Pathway of BMS-337044 from BMS-337039 (920008681 1.0)

Report-011228: In Vitro Metabolism of OPC-14597 by Liver Microsomes from Humans and Animals (920001396 1.0)

**Report-013109:** Identification of OPC-14597 Metabolite Produced by Human Liver Microsomes in Vitro (920003535 1.0)

**Report-010707:** Identification of OPC-14597 Metabolites in Humans and Rats (3) (920001392 1.2)

Comparative Biotransformation of [<sup>14</sup>C] Aripiprazole in Human, Monkey, Rat and Mouse Hepatocytes (930000129 1.0)

**Report-013611:** In Vitro Metabolism of OPC-14597 Using Human and Rabbit Liver Microsomes – The Check of the Production of DM-1456 from OPC-14597 (920010957 1.1)

**Report-010498:** In Vitro Metabolism of OPC-14597 by Microsomes from Human Lymphoblastoid Cell Line Transformed with Human Cytochrome P450 cDNAs (920001393 1.1)

Vol.1.36 (Pharm-Tox Vol. 24):

**Report-010945:** In Vitro Metabolism of OPC-14597 and Inhibition by OPC-14597 of Dextromethorphan Metabolism by Recombinant Human CYP2D6 and CYP3A4 (920001394 1.0)

**Report-011575:** Cytochrome P450 Isoforms Responsible for the OPC-14597 Metabolism by Human Liver Microsomes (920001356 1.0)

**Report-013604:** In Vitro Metabolism of OPC-14597, a Major Metabolite of OPC-14597 by Microsomes from Human B-Lymphoblastoid Cell Line Transformed with Human Cytochrome P450 cDNAs (920009202 1.1)

**Report-011801:** Inhibition of OPC-14597 on Dextromethorphan O-Demethylation Activities of CYP2D6 in Human Liver Microsomes (II) (920001357 1.0)

A Study to Assess the Potential for Inhibition of Human Cytochrome P450 by BMS-337039 and BMS-337044 (930000146 1.0)

A Study to Assess the Potential for Inhibition of Human Cytochrome P450 by BMS-337039 and BMS-337044 Utilizing Human Liver Microsomes and Marker Substrates (930000147 1.0)

### **Protein Binding Studies**

Vol.1.30 (Pharm-Tox Vol. 18):

In Vitro Determination of Protein Binding of BMS-337039 in Mouse, Rat, Rabbit, Monkey, Dog and Human Sera and of BMS-337044 in Human Serum (930000112 2.0)

[<sup>14</sup>C]OPC-14597 Human Plasma Protein Binding Method Validation Equilibrium Dialysis (920011155 1.1)

**Report-010398:** Determination of Human, Rat and Dog Serum Protein Binding of <sup>14</sup>C-OPC-14597 Using a Polydimethylsiloxane-Coated Glass Bead Assay (920001390 1.0)

**Report-012757:** In Vitro Protein Binding of OPC-14597 Metabolites, OPC-3373, DCP, OPC-14857 and DM-1452 in Human Serum (920001406 1.0)

**Report-013277:** The Blood-Plasma Partition Ratio of OPC-14597 in Rat, Mouse, Rabbit and Human (920007069)

*Report-013353: The Blood-Plasma Partition Ratio of OPC-14597 in Cynomolgus Monkeys (920007071 1.0)*

**Dissolution Method Development and Dissolution Data**

Vol. 1.4: Validation of the Dissolution Method (pH 1.2) for Aripiprazole

Vol. 1.5: Primary Lots/Supporting Lots

- Validation of the Dissolution Method (pH4.0) for Aripiprazole Tablets
- Protocol Summary for "Bridging" Study of Dissolution Methods for Aripiprazole Tablets
- Interim Study Results for the Bridging Study of Dissolution Methods for Aripiprazole Tablets

**APPEARS THIS WAY  
ON ORIGINAL**

**Office of Clinical Pharmacology and Biopharmaceutics**  
**New Drug Application Filing and Review Form**

General Information About the Submission				
Information		Information		
NDA Number	21-436	Brand Name	ABILITAT?	
OCPB Division (I, II, III)	DPE-I	Generic Name	Aripiprazole	
Medical Division	HFD-120 (Neuropharm)	Drug Class	quinolinone	
OCPB Reviewer	Zhao, Hong	Indication(s)	Schizophrenia	
OCPB Team Leader	Baweja, Raman	Dosage Form	Tablet	
		Dosing Regimen	15 mg QD, highest effective dose-30 mg QD	
Date of Submission	10/31/01	Route of Administration	Oral	
Estimated Due Date of OCPB Review	6/1/02	Sponsor	Otsuka/BMS	
PDUFA Due Date	8/31/02	Priority Classification	S	
Division Due Date	6/15/02			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:	X	2		
Isozyme characterization:	x	18		
Blood/plasma ratio:	X	2		
Plasma protein binding:	X	4		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	5		
multiple dose:	X	3		
Patients-				
single dose:	X	1		
multiple dose:	X	4		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	x	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	5		
In-vivo effects of primary drug:	x	4		
In-vitro:	x	3		
Subpopulation studies -				
ethnicity:				
gender:	x	1		
pediatrics:	x	1		
geriatrics:	X	1		
-- renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:	X	1		
Phase 3:	X	1		
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		
Phase 3 clinical trial:	x	2		
Population Analyses -				
Data rich:				

Data sparse:	x	1		
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:	X	1		
Relative bioavailability -	X	3		
solution as reference:	X	1		
alternate formulation as reference:	X	3		
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	IV			
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:	X	2		
Chronopharmacokinetics	X	1		
Pediatric development plan				
Literature References				
Total Number of Studies		48		
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application fileable ?	x	Reasons if the application is <u>not</u> fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	See attached Review.	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Whether dosage adjustments are needed for special populations (CYP2D6 poor metabolizers, hepatic or renal impairment, coadministration of CYP3A4 or CPY2D6 substrates or inhibitors, etc.)?  Can the highest strength (30 mg) which has not been used in any PK or clinical studies, be approved based on in vitro data?			
Other comments or information not included above	Request for Pharmacometrics consult:  This NDA has one report of population PK/PD analysis of aripiprazole (vol.84). Pharmacometrics consult is requested.			
Primary reviewer Signature and Date	Hong Zhao, 12/18/01			
Secondary reviewer Signature and Date	Raman Baweja, 12/18/01			

CC: NDA 21-436, HFD-850 (Electronic Entry or Lee), HFD-120 (CSO), HFD-860 (Zhao, Baweja, Mehta), CDR (Biopharm-CDR)

*Office of Clinical Pharmacology and Biopharmaceutics*  
**Pharmacometrics Consult Request Form**

<b>NDA:</b>	21-436	<b>Sponsor:</b>	Otsuka/BMS
<b>IND:</b>			
<b>Brand Name:</b>	Abilitat	<b>Priority Classification:</b>	S
<b>Generic Name:</b>	Aripiprazole	<b>Indication(s):</b>	Schizophrenia
<b>Dosage Form:</b>	Oral Tablets	<b>Date of Submission:</b>	10/31/01
<b>Dosing Regimen:</b>	15 mg QD, up to 30 mg QD	<b>Due Date of PM Review:</b>	4/30/02
<b>Division:</b>	DPE-1	<b>Medical Division:</b>	HFD-120, Neuropharm
<b>Reviewer:</b>	Hong Zhao	<b>Team Leader:</b>	Raman Baweja

Tabular Listing of All Human Studies That Contain PK/PD information (This can be requested at the pre-NDA stage as indicated on the PM roadmap)  
(may attach tabular summary of all studies from NDA to this document)

See attached NDA filing review.

**List the following for this compound (if known. The list will be confirmed by PM Scientist during the review):**

<b>Clinical endpoint(s):</b>	Total PANSS score
<b>Surrogate endpoint(s):</b>	
<b>Biomarker(s):</b>	
<b>Any reported optimal dose based on PK/PD ?:</b>	No
<b>Any reported dose/concentrations associated with efficacy/ toxicity ?:</b>	No
<b>Principal adverse event(s):</b>	Orthostatic hypotension (1.2%) Somnolence (11%) 4 beats/min (median) increase in heart rate) compared to 1 beat/min increase for placebo group.

Pharmacometrics Request: (Jointly filled out with PM Scientist)

(Briefly state the objective(s) of the consult. The request should be as explicit as possible, and should state whether a review or additional analysis is needed. An assessment of the impact that the data will have on labeling should be included (Questions to be answered in QBR). The proposed labeling and the HPK Summary along with the relevant volumes should be available to the PM Scientist.)

This NDA has one population PK/PD analysis of aripiprazole in schizophrenia patients (Vol. 84).

The objectives of this population PK analysis were

- (1) To describe the PK of aripiprazole in patients with schizophrenia.
- (2) To identify predictors of exposure to the drug (demographics, laboratory values, concomitant medications, disease, etc.) and identify sub-populations with altered PK.
- (3) To estimate the inter-individual and residual variability of aripiprazole pharmacokinetics.

The PK data file for analysis contained 2563 plasma samples of 694 patients from the following 5 studies:

**31-93-202:** Efficacy and Tolerability of Ascending Doses of OPC-14597 Compared to Placebo and to Haloperidol in Acutely Relapsing Hospitalized Schizophrenic Patients (34 patients, 175 concentrations)

**31-94-202:** A Dose Ranging Study of the Efficacy and Tolerability of OPC-14597 in Acutely Relapsing Hospitalized Schizophrenic Patients (180 patients, 1255 concentrations)

**31-97-201:** A Phase III Double-Blind Placebo-Controlled Study of Aripiprazole in the Treatment of Psychosis (204 patients, 631 concentrations)

**31-97-202:** A Phase III Double-Blind Placebo-Controlled Study of Aripiprazole in the Treatment of Psychosis, with Risperidone as Active Control (202 patients, 664 concentrations)

**31-97-203:** An Open-Label Follow-on Study of the Long-Term Safety of Aripiprazole in Patients with Psychosis (515 patients, 1501 concentrations)

The objectives of the population PK/PD analysis were

- (1) To assess the relationship between PD (as measured by a decrease from baseline in the total PANSS score) versus systemic exposure, duration of treatment and covariates.
- (2) To estimate the inter-individual variability of aripiprazole pharmacodynamics.

The PK/PD file contributed 2472 total PANSS scores from 582 aripiprazole patients and 1205 scores from 306 placebo patients in 4 studies (Open-label Study 31-97-203 was not used).

The objective of the population PK/Safety analysis of aripiprazole was to assess the relationship between patients' aripiprazole plasma concentrations and QTc prolongation.

The data from the Studies 31-97-201 and 31-97-202 were used for the PK/Safety analysis. The data included 251, 506 and 616 QTc observations from respectively 184, 313 and 328 aripiprazole patients in the 2-hour, 12-hour and 48-hour window (the maximum time difference between ECG and blood draw).

## Summary

### Population PK Analysis

- The PK of aripiprazole were described by a linear one-compartment model with first order absorption.
- Although clearance was related to lean body weight, and volume of distribution was related to weight and age, these dependencies are unlikely to be clinically important.
- The estimates of the apparent oral clearance in patients were similar to those for normal volunteers.
- The results of the analysis indicated that no dose adjustments are needed based on demographic variables.
- Although the analysis indicated no dosage adjustment for any of the medications co-administered with aripiprazole, the number of patients on the concomitant medications, except benzodiazepines, was too small to be conclusive.

### PK/PD Analysis

- The change from baseline of the total PANSS score in patients taking aripiprazole was described as the sum of change due to placebo and change due to the aripiprazole. Both effects (decrease from baseline) increased with duration of dosing during the study.

- The placebo effect increased with increasing baseline score, and was lower in patients who were administered lorazepam concomitantly.
- The total effect of the drug (placebo and aripiprazole effect) was significantly higher in patients with higher baseline score, and lower in patients with concomitant lorazepam administration.
- The modeling indicated that neither exposure nor dose was found to be correlate well with the efficacy of aripiprazole.

**PK/Safety Analysis**

- No relationships could be determined between the change from baseline of  $QTC_B$ ,  $QTC_F$  or  $QTC_n$  and the corresponding plasma concentrations of aripiprazole.
- There was no prolongation of  $QT_c$  in patients on aripiprazole, regardless of the algorithm used to calculate  $QT_c$ .
- The variability in changes from baseline of  $QT_c$  in aripiprazole patients was comparable to that in placebo patients.

Pharmacometrics consult is requested to verify the information generated from these population PK or PK/PD or PK/Safety analyses that has impacts on labeling.

**Due Date to the Reviewer 4/30/02**

**Primary Reviewer Hong Zhao      Signature \_\_\_\_\_      Date 12/18/01**

**Team Leader Raman Baweja      Signature \_\_\_\_\_      Date 12/18/01**

**PM Scientist Jogarao Gobburu      Signature \_\_\_\_\_      Date \_\_\_\_\_**

**CC: HFD-860 (Mehta, Baweja, Zhao, Gobburu) HFD-850 (Lee)**

**APPEARS THIS WAY  
ON ORIGINAL**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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NDA: 21-436	Submission Date(s): 10/31/01, 12/21/01, 2/27/02, 3/29/02, 4/4/02, 5/9/02
Brand Name	ABILITAT
Generic Name	Aripiprazole
Reviewer	Hong Zhao
Team Leader	Raman Baweja
Pharmacometrics Reviewer	Gene Williams
Team Leader	Jogarao Gobburu
OCPB Division	DPE 1 (HFD-860)
ORM Division	DNDP (HFD-120)
Sponsors	Otsuka Pharmaceutical Co., Ltd. Bristol-Myers Squibb Company
Relevant IND(s)	_____
Submission Type; Code	NME, 1S
Formulation; Strength(s)	Tablets, 2-, 5-, 10-, 15-, 20-, 30-mg
Indication	Treatment of Schizophrenia

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## **1 Executive Summary**

### **1.1 Recommendation**

This submission (NDA-21-436) for Aripiprazole Tablets (ABILITAT) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting the OCPB requirements.

The sponsor is requested to perform drug-drug interaction studies as outlined in the Comments to Clinical Division, and a food effect study on the highest tablet strength (30-mg) as Phase IV commitment. The sponsor is requested to adopt the OCPB labeling as provided in this review. Also, the sponsor is requested to adopt the dissolution methodology and specification for all six strengths of aripiprazole tablets, as outlined in the Comments to the Sponsor.

### **Comments to Clinical Division**

Aripiprazole is mainly eliminated by metabolic clearance with three biotransformation pathways and both CYP2D6 and CYP3A4 are responsible for dehydrogenation and hydroxylation, and CYP3A4 responsible for *N*-dealkylation. Dehydrogenation generates

the active metabolite OPC-14857 which is equally potent as the parent drug with systemic exposure being 40% of the parent drug.

***With regard to recommending dosage adjustment, the following issues caught OCPB's attention:***

- (1) In the proposed labeling for aripiprazole, the sponsor did not mention the effect of CYP2D6 genotype (PM and EM) on aripiprazole pharmacokinetics. In the NDA, the sponsor claims that "The magnitude of the increase for aripiprazole plasma concentrations was complementary to the magnitude of the decrease for OPC-14857 (metabolite). As aripiprazole and OPC-14857 have comparable affinity to the D<sub>2</sub> receptor and display similar protein binding, the effects of CYP2D6 PM genotype are not expected to result in a change in the safety or efficacy profile of aripiprazole."
- (2) Under Drug Interactions section of the labeling, it states "consideration should be given to reducing the dosage in patients who are on multiple concomitant medications that inhibit CYP3A4 and/or CYP2D6 enzymes".
- (3) Also, in Drug Interactions section of the labeling, the effect of carbamazepine, a potent CYP3A4 inducer is not mentioned.
- (4) Under Special Population of the labeling, for Hepatic impaired patients, the sponsor states: "..., a study in ... did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and OPC-14857." No dosage adjustment is recommended for hepatically impaired patients.

**OCPB Recommends dosage adjustment for all conditions that will result in a significant increase in drug exposure because there were some aripiprazole dose-related adverse events as outlined below:**

- (a) Although in the recommended dose range (15-30 mg), QT<sub>c</sub> increase was not correlated to dose, at doses greater than 30 mg (45-90 mg/day) larger increase of QT<sub>c</sub> was observed.
- (b) For overall somnolence incidence, placebo-7.7%, 15 mg-8.7%, 20 mg-7.5%, and 30 mg-15.3%. Also, 25-30 mg/day in elderly patients were generally safe but marginally tolerated due to persistent somnolence that extended even beyond the dosing period in some patients.
- (c) By visual inspection of the incidence of treatment-emergent AEs by dose in the four fixed-dose placebo controlled studies, it appeared to be dose-related for several other AEs: asthenia, orthostatic hypotension, tachycardia, akathisia, lightheadedness, tremor, blurred vision, and stiffness although the apparent dose relationship was not consistent across studies and in some cases was driven by the results of only one study.

- (d) In Study 99224 (doses up to 90 mg/day), increased incidences of akathisia and tachycardia were seen in the highest dose group (90-mg/day); 55% of 40 patients reported an EPS (extrapyramidal symptoms) related adverse event, with the highest incidence occurring in the 90-mg dose group (6 patients, 86%); prolactin level decreased in 30- and 45 mg dose groups but increased moderately in 60 to 90 mg groups with the highest in 90-mg group.

**Genotype:** There were 82% increase in aripiprazole systemic exposure and 34% decrease in the active metabolite OPC-14857 exposure in CYP2D6 poor metabolizers (PM) compared to the extensive metabolizers (EM). Based on the fact that the metabolite to the parent ratio is 0.4 and both moieties are considered equally potent, the net increase of aripiprazole exposure is greater than 60%. The total body clearance of aripiprazole in PMs decreased by 40%. The efficacy and safety of aripiprazole have not been adequately studied in PM patients. Also, concomitant administration of potential inhibitors of CYP3A4 with aripiprazole in CYP2D6 PMs has not been studied.

**Selective Inhibitors of CYP2D6:** Co-administration of aripiprazole with CYP2D6 inhibitors (Quinidine, 166 mg/day) increased aripiprazole plasma concentrations in EM subjects to exposures similar to those observed in PM subjects (clearance decreased by 52%). Aripiprazole dose should be reduced to at least one-half of its normal dose when adding potential CYP2D6 inhibitors such as quinidine to aripiprazole drug therapy in patients with CYP2D6 EM status.

**Selective Inhibitor of CYP3A4:** Co-administration of aripiprazole with ketoconazole (200 mg/day) decreased the clearance of aripiprazole and its active metabolite OPC-14857 by 40% and 44%, respectively. The worst-case scenario involving the higher clinical dose of ketoconazole (400 mg/day) added to aripiprazole at steady state has not been studied. If concomitant administration of aripiprazole and ketoconazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose.

- The sponsor should investigate the effect of potent CYP3A4 and CYP2D6 inhibitors at maximum clinical doses on aripiprazole pharmacokinetics in CYP2D6 extensive metabolizers.
- The sponsor should also investigate the effect of potent CYP3A4 inhibitor at maximum clinical dose on aripiprazole pharmacokinetics in CYP2D6 poor metabolizers.

**Carbamazepine:** Although the data came from only three patients (ongoing study), coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole resulted in more than 50% decrease in  $C_{max}$ ,  $C_{min}$  and AUC values of both aripiprazole and the active metabolite OPC-14857, and nearly 2-fold increase in aripiprazole clearance. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be increased, and when carbamazepine is withdrawn from the combination therapy, aripiprazole dose should be reduced.

**Hepatic Impairment:** There were no clear trends as to how the degrees of HI affect aripiprazole pharmacokinetics. The pharmacokinetic result of this study was complicated by concomitant medication (spironolactone) with 4 subjects (mild and moderate HI) having aripiprazole terminal half-life greater than 240 hours. The maximum decreases in aripiprazole total clearance and unbound clearance were 25% and 37%, respectively, which was observed in the mild HI group. No dosage adjustment is recommended for HI due to pharmacokinetics changes. However, 3 out of 19 subjects with HI had potential clinically significant ECG changes, aripiprazole should be used with caution in patients with hepatic impairment.

***With regard to recommending starting dose:***

In clinical efficacy trials, no increased efficacy was achieved with aripiprazole doses higher than 15 mg/day and no lower fixed dose than 10 mg/day was studied for efficacy. Although 10 mg/day was only studied in one well-controlled, adequately powered trial, it showed higher efficacy compared to 15 mg/day and 20 mg/day in the same study. *Should we recommend 10 mg/day as starting dose instead of 15 mg/day proposed by the sponsor?*

**Comments to the Sponsor**

***Dissolution method and Specification***

The sponsor is requested to adopt the following dissolution method and specification for all strengths of ABILITAT tablets (2-, 5-, 10-, 15-, 20- and 30-mg):

Apparatus: USP Apparatus 2 (paddles) at 60 rpm  
Medium: 0.1 N HCL (pH 1.2) at 37±0.5 C°  
Specification: \_\_\_\_\_, in 30 min

**1.2 Phase IV Commitments**

Food effect study was conducted on the 15-mg dose strength. Due to the limited solubility of aripiprazole and non-rapid dissolving nature of the tablet in gastric pH (pH 1.2), food effect should be studied on the highest strength (30 mg).

Hong Zhao, Ph.D. \_\_\_\_\_

RD/FT Initiated by Raman Baweja, Ph.D. \_\_\_\_\_

OCPB Briefing on August 2, 2002

Attendees: Thomas Laughren, Gregory Dubitsky, Robert Harris, Lois Freed, Henry Malinowski, Barbara Davit, Patrick Marroum, Raman Baweja, Gobburu Jogarao, Gene Williams, Hong Zhao, Nhi Nguyen, Andre Jackson, Anne Zajicek, Meiling Chen.

Cc: NDA21-436 (Aripiprazole Tablets), HFD-120, HFD-860 (Zhao, Baweja, Mehta),  
Central Documents Room (Biopharm-CDR)

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**List of Clinical Studies for Pharmacokinetics, Pharmacodynamics and Metabolism of Aripiprazole,  
By Study Characteristics**

<b>Study Characteristics</b>	<b>Protocol Number</b>	<b>Dosage Form</b>
<b>Drug Disposition</b>		
14		
Absolute bioavailability	CN138-016	Tablet
Biliary Metabolite Excretion	CN138-061	Tablet
<b>Safety and Pharmacokinetics</b>		
Multiple Ascending Dose Healthy Subjects	31-93-201	Tablet
Multiple Titrated Dose Healthy Subjects	31-93-204	Tablet
Diurnal Variation Healthy Subjects	31-98-201	Tablet
Pilot High Dose in Schizophrenic Subjects I	31-98-202	Tablet
Pilot High Dose in Schizophrenic Subjects II	31-99-224	Tablet
Pharmacodynamics in Healthy Subjects	31-94-201	Tablet
Population Pharmacokinetics and Pharmacodynamics in Schizophrenic Subjects	31-00-233	Tablet
<b>Special Populations</b>		
Age/Gender	31-00-225	Tablet
Renal Impairment	31-98-208	Tablet
Hepatic Impairment	31-98-205	Tablet
Pediatric/Adolescent in Patients with Conduct Disorder	CN138-014	Tablet
Elderly with Dementia	31-98-203	Tablet
<b>Food and Drug Interactions</b>		
Food Effect (Standard High Fat)	CN138-018	Tablet
Dextromethorphan I	31-97-205	Tablet
Dextromethorphan II	31-00-231	Tablet
Warfarin	CN138-043	Tablet
Omeprazole	31-00-232	Tablet
Famotidine	31-00-226	Tablet
Activated charcoal	31-00-227	Tablet
Ketoconazole	31-98-206	Tablet
Quinidine	31-98-207	Tablet
Carbamazepine	CN138-022	Tablet
Valproate	CN138-023	Tablet
Lithium	CN138-021	Tablet
Ethanol	31-00-230	Tablet
<b>Formulation Support</b>		
Monohydrate Bioequivalence I	CN138-015	Tablet
Monohydrate Bioequivalence II	CN138-034	Tablet
Proposed Commercial Bioequivalence	CN138-054	Tablet
Dose Strength Equivalence	CN138-035	Tablet
Dose Strength Equivalence	CN138-065	Tablet

### 3 Summary of CPB Findings

#### Clinical Pharmacology Program

The aripiprazole clinical pharmacology program comprised of 35 clinical studies:

- 25 studies conducted in healthy subjects, including 3 safety/pharmacokinetic studies, 1 pharmacodynamic study involving positron emission tomography, 3 drug disposition studies, 1 food interaction study, 9 drug interaction studies (ketoconazole, quinidine (CYP2D6 EMs and PMs), dextromethorphan, pH effect (famotidine), activated charcoal, omeprazole, warfarin, ethanol), 7 bioavailability or bioequivalence studies and 1 age/gender study.
- 6 studies in patients with schizophrenia or schizoaffective disorder, including 2 safety/pharmacokinetic studies, 1 population pharmacokinetic analysis, and 3 drug interaction studies (carbamazepine, lithium, divalproex).
- 4 safety/pharmacokinetic studies in patients with hepatic impairment, patients with renal impairment, elderly subjects with dementia, and children/adolescents with conduct disorder.
- 7 pharmacology studies have been conducted in Japan. In these studies, pharmacokinetics of aripiprazole were assessed in a lower dose range, 0.25-6 mg in healthy male Japanese subjects, in contrast to the 5-30 mg dose range used supporting this application.

In addition, *in vitro* metabolic study reports and protein binding study reports are included in Nonclinical Pharmacology and Toxicology section of the submission. Dissolution method development and data are provided in Chemistry section of the submission.

#### Metabolism and Genotype

**Metabolism:** In humans, aripiprazole is primarily metabolized by three biotransformation pathways: dehydrogenation, *N*-dealkylation, and hydroxylation. The enzymes responsible for the three primary biotransformation pathways in humans were determined by *in vitro* metabolism studies with recombinant human cytochrome P450 isoforms and human liver microsomes. Both CYP3A4 and CYP2D6 were responsible for dehydrogenation and hydroxylation; whereas, *N*-dealkylation was catalyzed by CYP3A4. Other CYP isoforms, namely 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2E1, were not involved in the metabolism of aripiprazole. The binding affinities of several aripiprazole metabolites for D<sub>2</sub> and D<sub>3</sub> receptors were determined along with the ratio of their molar AUC to that of aripiprazole during administration of 30 mg/day in healthy subjects or schizophrenia patients. Based on the AUC ratio of the dehydrogenated metabolite OPC-14857 to aripiprazole of 0.40 and its comparable binding affinity to D<sub>2</sub> and D<sub>3</sub> receptors, this metabolite may contribute to the pharmacological activities of aripiprazole. Since this ratio was less than 0.002 for other metabolites, it is unlikely that other metabolites contribute to the pharmacological effect of aripiprazole.

**Genotype:** Following a single 10 mg dose of aripiprazole, CYP2D6 poor metabolizers (PM, N=5) had a similar C<sub>max</sub> but an 82% higher systematic exposure (AUC<sub>∞</sub>) and 41% lower clearance of aripiprazole than that of the CYP2D6 extensive metabolizers (EM,

N=12). Plasma exposure of the active metabolite, OPC-14857 was decreased by 34% in the PM subjects relative to the EM subjects. If OPC-14857 and aripiprazole are considered equally potent, there was a 65% net increase in aripiprazole systemic exposure in PM subjects. The sponsor claims that the effects of CYP2D6 PM genotype are not expected to result in a change in the safety or efficacy profile of aripiprazole, therefore no dose adjustment is routinely required based on CYP2D6 metabolism genotype or phenotype. In fact, the efficacy, safety and pharmacokinetics of aripiprazole have not been adequately studied in PM patients.

#### **Basic Pharmacokinetic Information**

Aripiprazole is well absorbed after oral administration, with peak plasma concentrations occurring within 3-5 hours after dosing. The absolute oral bioavailability of the tablet formulation of aripiprazole is 87%. The terminal half-life of aripiprazole is long, averaging 75 hours. Steady-state concentrations of aripiprazole are attained within 14 days of once daily dosing. In healthy subjects, the steady-state  $C_{max}$  and AUC increased linearly and proportionally to doses ranging from 5 to 30 mg. In schizophrenic patients, the pharmacokinetics of aripiprazole appeared to be linear at doses ranging from 30-75 mg per day. The steady-state accumulation index of aripiprazole was 5, which is predictable from single dose pharmacokinetics. Aripiprazole was widely distributed into tissues ( $V_d=4.94$  L/kg after i.v. dosing) despite plasma protein binding in excess of 99%. Aripiprazole is mainly metabolized with less than 1% of an oral dose excreted unchanged in urine and 18% unchanged in the feces. Approximately 26% of the radiolabeled dose was recovered in the urine and 55% in the feces. The major metabolite OPC-14857 with an elimination half-life of 94 hours, is approximately 40% of the parent drug exposure in plasma and has similar pharmacologic activity as the parent drug.

#### **Population Pharmacokinetic Analysis**

Population pharmacokinetic analysis was performed using NONMEM on data from several Phase II and Phase III studies. Several demographic, laboratory and disease parameters were examined to see if they had an influence on aripiprazole concentrations. The pharmacokinetics of aripiprazole were described by a linear one-compartment model with first-order absorption. The covariates examined were gender, age, race (Caucasian, Black, Hispanic, Asian, other), weight, body surface area, body mass index, lean body weight, smoking, alcohol consumption, differentiation between schizophrenia and schizoaffective disorder, creatinine clearance, total protein, creatine kinase, total bilirubin, alkaline phosphate, aspartate aminotransferase, and alanine aminotransferase. According to the sponsor, the results of the analysis indicated that no dose adjustment is needed based on demographic variables. Although clearance was moderately related to lean body weight, and volume of distribution was related to weight and age, these dependencies are unlikely to be clinically important. The estimates of the apparent oral clearance in patients were similar to those for normal volunteers and there is no difference in the pharmacokinetics of aripiprazole between healthy subjects and patients with schizophrenia. The analysis done by the OCPB Pharmacometrics Reviewer has found a 22% increase in aripiprazole clearance for smokers relative to non-smokers. No dose adjustment is required based on race, gender or smoking status.

### **Pharmacokinetic/Pharmacodynamic Analysis**

**Efficacy** – Based on the results provided by the sponsor, broad efficacy was established across a variety of endpoints with an onset of action as early as Week 1 for positive symptoms at doses of 15 mg and higher. The efficacy of doses of 15 mg and higher was established in two studies whereas the efficacy of the 10-mg dose was only established in one study. There is no evidence that doses higher than 15 mg QD are associated with increased efficacy, and 30 mg QD has been established as an effective dose and is the highest dose that has been systematically evaluated in clinical trials. The PK/PD modeling indicated that neither exposure nor dose was found to be correlated well with the efficacy of aripiprazole. Rather, PANSS score was a function of baseline PANSS score, duration of treatment and concomitant lorazepam administration. The median decrease in PANSS score for patients with a median baseline of 93 was 18.2 points in the absence of lorazepam and 14.5 points with co-administration of lorazepam.

**Binding to D<sub>2</sub> Receptors:** After taking aripiprazole for 2 weeks, there was a dose dependent reduction in the binding of <sup>11</sup>C-raclopride, a specific D<sub>2</sub> receptor ligand, to the caudate and putamen detected by positron emission tomography (the D<sub>2</sub> receptor occupancy was 23%-46% for the 0.5 mg/day dose group which increased to 81% -95% for the 30 mg/day dose group). These results demonstrate that aripiprazole penetrates into the human central nervous system and supports the doses (2-30 mg/day) that were assessed in the Phase II/III studies.

**Safety** - A linear mixed-effects regression model for change of QT<sub>c</sub> from baseline versus aripiprazole concentration was fitted to the data. Separate models were fitted to each time window and heart rate correction method (Bazett, Federicia and fractional exponent), as well as for all data combined. The variability in QT<sub>c</sub> changes from baseline of patients on aripiprazole were similar to those on placebo. The slope of concentration effect was not statistically significant for any of the regressions. These analyses, therefore, concluded that no relationship existed between change from baseline in QT<sub>c</sub> and plasma concentration of aripiprazole, regardless of the heart rate correction formula and time window selected for analysis. Rather than use the common correction factors, the OCPB Pharmacometrics Reviewer used a population modeling approach to arrive at corrected QT values and a similar conclusion was reached: no change in corrected QT as a function of aripiprazole dose or concentration could be detected.

### **Pharmacokinetics in Special Populations**

**Gender:** Gender effect study revealed that C<sub>max</sub> and AUC of aripiprazole and its active metabolite OPC-14857 were 30-40% higher in women than in men, however, these differences were largely explained by differences in body weight (25%) between men and women.

**Elderly:** Age effect study revealed that aripiprazole clearance decreased by 20% in elderly (≥65 yrs) subjects compared to younger adult subjects (18-64 yrs) following a single 15 mg dose. However, there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenic patients. In addition, the pharmacokinetics of aripiprazole during multiple dose administration to elderly patients with dementia

appeared similar to that observed in young healthy subjects. Placebo-controlled studies of aripiprazole in schizophrenia did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from young subjects.

**Pediatric Population:** Children (6-12 yrs) with conduct disorder were found to have a 34% lower steady-state oral clearance of aripiprazole than adolescents (13-17 yrs) with conduct disorder or healthy adult subjects. This reduction in clearance disappeared when oral clearance was normalized to total body weight. The safety and effectiveness of ABILITAT for the treatment of schizophrenia in pediatric and adolescent patients has not been established.

**Hepatic Impairment:** Following a single 15 mg dose, there were no clear trends as to how the degrees of mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) affect aripiprazole pharmacokinetics. The pharmacokinetic result was complicated by concomitant medication (spironolactone) with 5 out of 7 subjects (mild and moderate HI) having aripiprazole elimination half-life greater than 240 hours. More importantly, 3 out of 19 subjects with hepatic impairment had ECG changes that met the criteria for potential clinically significant abnormalities: two subjects experienced QT<sub>c</sub> prolongation to 451 msec and 475 msec, respectively on Day 6 and one suffered first degree AV block on Day 1 after the single dose of aripiprazole. Therefore, aripiprazole should be used with caution in subjects with hepatic impairment.

**Renal Impairment:** After a single 15 mg dose of aripiprazole, C<sub>max</sub> of aripiprazole and OPC-14857 increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for OPC-14857 in subjects with severe renal impairment (creatinine clearance ≤30 ml/min) compared to that in healthy subjects. Although exposure of OPC-3373 were 26-fold higher and urinary excretion was 2-fold lower in subjects with severe RI compared to healthy subjects, the increased exposure of OPC-3373 was only 5% of aripiprazole exposure. No dose adjustment is routinely required in subjects with renal impairment.

### Drug Interactions

#### **Effects of Other Drugs on Aripiprazole**

Since *in vitro* studies showed that CYP3A4 and CYP2D6 were the primary isozymes responsible for aripiprazole metabolism, clinical drug interaction studies were conducted.

**Ketoconazole** - Following a single 15 mg dose of aripiprazole to 18 healthy subjects, ketoconazole (200 mg/day), a potent inhibitor of CYP3A4, decreased the oral clearance of aripiprazole and its active metabolite OPC-14857 by 40 and 44%, respectively. The worst-case scenario which means the administration of higher clinical dose (400 mg/day) of ketoconazole has not been studied.

**Quinidine** - Following a single 10 mg dose of aripiprazole to 12 healthy subjects, quinidine (166 mg/day), a potent inhibitor of CYP2D6, decreased oral clearance of aripiprazole by 52% and decreased plasma concentrations of OPC-14857 by 34%.

**Population PK Analysis:** To further investigate the clinical relevance of coadministration of potent CYP2D6 and CYP3A4 inhibitors a population pharmacokinetic analysis of data from five Phase II and Phase III studies was conducted. Groups of concomitant medications, including substrates and inhibitors of CYP3A4 and CYP2D6 isozymes, were evaluated as covariates in the model. This analysis did not detect a significant effect on aripiprazole pharmacokinetics when these medications are co-administered.

- In an ongoing clinical study, coadministration of

**Lithium-** Coadministration of therapeutic doses of lithium (1200-1800 mg/day) for 21 days to patients with schizophrenia or schizoaffective disorder with 30 mg QD aripiprazole had no clinically significant effect on the pharmacokinetics of aripiprazole or OPC-14857 ( $C_{max}$  and AUC increased by less than 20%).

**Valproate -** Coadministration of therapeutic doses of valproate (350-1500 mg/day) for 21 days to patients with schizophrenia or schizoaffective disorder with 30 mg QD aripiprazole decreased aripiprazole  $C_{max}$  and AUC by 25% and increased its CL by 32%.

The sponsor claims that there was no evidence of EEG findings suggestive of epileptiform activity, encephalopathy, or other pathological EEG rhythms with the co-administration of lithium, valproate or carbamazepine with aripiprazole supporting the safety of these combinations.

#### **Effects of Aripiprazole on Other Drugs**

Based on the high ratio of the *in vitro*  $IC_{50}$ s to unbound maximum plasma concentrations of aripiprazole and its metabolite OPC-14857 (>1196), aripiprazole is not expected to significantly inhibit the *in vivo* activity of CYP1A2, 2C9, 2C19, 2D6, and 3A4 at clinically relevant plasma concentrations. A series of drug interaction studies with various marker CYP substrates (dextromethorphan-CYP2D6 and CYP3A4, warfarin-CYP2C9, omeprazole-CYP2C19) were conducted to investigate the potential of aripiprazole on the metabolism of other drugs. These studies administered aripiprazole for 14 days, to achieve steady-state pharmacokinetic conditions, at doses ranging from 10-30 mg/day. The results confirmed that aripiprazole has low potential to affect the pharmacokinetics of medications metabolized by CYP2C9, 2C19, 2D6, and 3A4.

**Alcohol-** Blood ethanol concentrations, performance of gross motor skills and stimulus response were not significantly different between ethanol co-administered with aripiprazole and ethanol co-administered with placebo.

**Activated Charcoal:** Activated charcoal administered one hour after a single 15 mg dose of aripiprazole to 9 healthy subjects decreased plasma aripiprazole and OPC-14857 concentrations by 54%, which suggests that this treatment may be effective for overdose.

#### **Food Effect and Stomach pH Effect**

**Food Effect:** Following a single 15 mg dose, a high fat meal increased  $C_{max}$  and AUC of aripiprazole and OPC-14857 by less than 20% and delayed their  $T_{max}$  by 3 hours. Due to the limited solubility of aripiprazole and non-rapid dissolving nature of the tablet in gastric pH, food effect study should be conducted on the highest strength (30-mg).

**Gastric pH Effect:** A single 40 mg dose of the  $H_2$  antagonist famotidine, a potent gastric acid blocker, influenced the solubility of aripiprazole and hence its absorption:  $C_{max}$  of aripiprazole and OPC-14857 decreased by 37% and 21%, respectively.

#### **Bioequivalence and Biowaiver**

Dosage strengths of 2-, 5-, 10-, 15-, 20-, and 30-mg are proposed for registration. The tablet strengths of 5-, 10- and 15-mg were used in clinical trials. There are minor changes in formulation composition and similar dissolution performance was seen between the tablets used in clinical pharmacology and Phase II/III studies versus those intended for marketing. Bioequivalence studies were conducted between 1x15 mg trade tablets and 3x5 mg trade tablet, and between 1x30 mg trade tablet and 3x10 mg trade tablets in healthy subjects where the bioequivalence criteria were met. A biowaiver is requested for strengths lower than 30-mg based on following facts: (1) the pharmacokinetics of aripiprazole is linear (5-30 mg); (2) the 30 mg tablet is bioequivalent to 3x10 mg tablets; (3) the lower strengths are compositionally proportional to the 30 mg strength; and (4) similar dissolution performance of these tablets in 0.1 N HCl, pH 4.0 buffer and pH 6.8 buffer was observed. Therefore, the biowaiver for lower strengths of aripiprazole tablets can be granted.

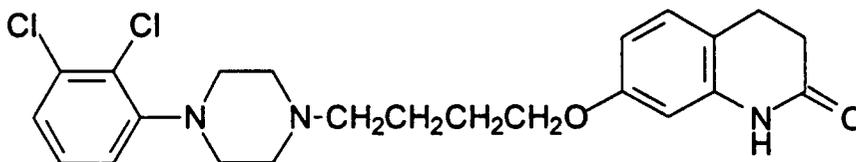
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## 4 QBR

### 4.1 General Attributes

1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?*

- ABILITAT (aripiprazole) is a novel antipsychotic agent with unique pharmacologic properties and a chemical structure that differs from current antipsychotic agents. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydro-2(1H)-quinolinone. The empirical formula is  $C_{23}H_{27}Cl_2N_3O_2$  and its molecular weight is 448.39. The chemical structure is:



- ABILITAT™ (aripiprazole) is available as tablets in 10-mg, 15-mg, and 30-mg strengths for oral administration. Inactive ingredients include: lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include ferric oxide (yellow or red).

**Dosage and Administration:** The recommended starting dose for ABILITAT is 15 mg/day administered on a once-a-day schedule without regard to meals. There is no evidence that doses higher than 15 mg QD are associated with increased efficacy. 30 mg QD has been established as an effective dose and is the highest dose that has been systematically evaluated in clinical trials.

**Pediatric and Adolescent Use:** The safety and effectiveness of ABILITAT for the treatment of schizophrenia in pediatric and adolescent patients has not been established.

**Dosage in Special Populations:** Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment.

**Maintenance Therapy:** There is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it. Systematic evaluation of aripiprazole has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 30 mg/day. Patients should be maintained on the dose to which they respond. Patients should be periodically reassessed to determine the need for maintenance treatment.

**Switching from Other Antipsychotics:** According to the sponsor, data was prospectively and systematically collected to address the safety of switching from other antipsychotics to ABILITAT (30 mg/day). These data indicate that any of the following methods can be

used safely for switching patients to aripiprazole from another antipsychotic monotherapy:

- immediate discontinuation of the patient's current antipsychotic regimen and immediate initiation of aripiprazole;
- immediate initiation of aripiprazole while tapering off the current antipsychotic regimen over a 2-week period;
- upward titration of aripiprazole over a 2-week period and simultaneous tapering off of the patient's current antipsychotic regimen over the same 2-week period.

**Pharmacologic Class and Potential Clinical Benefits:** Aripiprazole is an atypical antipsychotic drug. It exhibits high to moderate affinity for various central neuroreceptors:

**Table 1. Aripiprazole Affinity to Central Neuroreceptors**

High Affinity		Moderate Affinity	
Receptor	K <sub>i</sub> (nM)	Receptor	K <sub>i</sub> (nM)
Dopamine D <sub>2</sub>	0.34	Dopamine D <sub>4</sub>	44
Dopamine D <sub>3</sub>	0.8	Serotonin 5-HT <sub>2C</sub>	15
Serotonin 5-HT <sub>1A</sub>	1.7	Serotonin 5-HT <sub>7</sub>	39
Serotonin 5-HT <sub>2A</sub>	3.4	α <sub>1</sub> -adrenergic	57
		Histamine H <sub>1</sub>	61
		Serotonin reuptake site	98
	Low affinity		
Muscarinic receptors	IC <sub>50</sub> >10μM		

Its mechanism of action differs from that of currently marketed typical and atypical antipsychotic drugs. Aripiprazole acts as a D<sub>2</sub> receptor partial agonist in functional studies. In animals, aripiprazole demonstrates agonist activity at dopamine (presynaptic) autoreceptors and at postsynaptic D<sub>2</sub> receptors, aripiprazole acts as an antagonist. However, the mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown. The sponsor claims that the unique profile of aripiprazole's interaction with central neuroreceptors also result in a favorable safety and tolerability profile with a low incidence of EPS (extrapyramidal symptoms), no elevation in prolactin levels, decreased adrenergic and anticholinergic side effects and decreased weight gain.

## 4.2 General Clinical Pharmacology

**1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?**

**Schizophrenia** - Schizophrenia is a major psychotic disorder with a lifetime prevalence of approximately 1% of the population, and a peak age of onset between 15 and 35 years. It follows a chronic course with intermittent relapses; during the short term phases, schizophrenia is characterized by psychological and behavioral symptoms that can be classified into positive (hallucination, delusions), negative (flat affect, social and emotional withdrawal, poverty of speech) and disorganized symptoms (disorganized

speech and behavior), thought distortion and poor attention. Schizophrenia patients have a suicide rate of about 10%.

**Response Endpoints** - Several instruments were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (**PANSS**) and Brief Psychiatric Rating Scale (**BPRS**) are both multi-item inventories of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The BPRS Psychosis Cluster (**Core Score**), a subset of the BPRS that can also be derived from the PANSS, is used to assess actively psychotic patients. The Clinical Global Impression (**CGI**) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

**Safety** – Laboratory safety tests, a physical exam, vital signs and blood pressure, 12-lead ECG were usually performed at screening, prior to dosing and upon exiting the study. A 12-lead ECG was also performed at 4 hours post-dose and on the day prior to discharge from the clinical unit. Adverse events were recorded. Serum prolactin concentrations were determined in some studies.

**2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?**

Aripiprazole is primarily metabolized by the liver via multiple biotransformation pathways and undergoes minimal pre-systemic metabolism. Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in systemic circulation. At steady state, OPC-14857, the active metabolite (dehydrogenation), represented about 40% of aripiprazole AUC in plasma.

The binding affinities of several aripiprazole metabolites for D<sub>2</sub> and D<sub>3</sub> receptors was determined along with the ratio of their molar AUC to that of aripiprazole during administration of 30 mg/day in healthy subjects or schizophrenia patients.

**Table 2. Binding Affinities and Molar Plasma AUC Ratios of Aripiprazole Metabolites to Dopamine D<sub>2</sub> and D<sub>3</sub> Receptors**

Metabolite	D <sub>2</sub> (K <sub>i</sub> , nM)	D <sub>3</sub> (K <sub>i</sub> , nM)	AUC Ratio (Metabolite/Aripiprazole)
Aripiprazole	0.3	0.8	1
OPC-14857	0.4	0.5	0.394
DM-1458	0.7	0.4	0.006
DM-1451	0.3	0.3	0.006
DM-1452	0.3	0.4	ND
DCPP	127	42	<LLQ
DM-1454	491	92	<LLQ
DM-1457	18%	15% binding @100 μM	ND
OPC-3952	no binding	no binding @ 100 μM	ND
OPC-3373	no binding	no binding @ 100 μM	0.010

Based on the AUC ratio of OPC-14857 to aripiprazole of 0.4 and its comparable binding affinity to D<sub>2</sub> and D<sub>3</sub> receptors, this metabolite may contribute to the pharmacological activities of aripiprazole. Also, based on the low AUC ratio of all other metabolites to aripiprazole (<0.002), it is unlikely that other metabolites contribute to the pharmacological effect of aripiprazole. Metabolites in the plasma were measured along with the parent drug to assess pharmacokinetic parameters, but exposure-response relationships were not explored for these metabolites.

**3. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?**

ABILITAT activity is primarily due to the parent drug aripiprazole, and to a lesser extent, of the active metabolite OPC-14857. The mean elimination half-life of aripiprazole is about 75 hours. Steady-state concentrations are attained within 14 days of dosing. Aripiprazole accumulation is predictable from single dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is primarily through hepatic metabolism, involving mainly two pathways (CYP2D6 and CYP3A4).

**Clinical Efficacy Trials** - The efficacy of ABILITAT in the treatment of schizophrenia was evaluated in five short-term (4- and 6-week), placebo-controlled trials of inpatients, four of which also included an active control group consisting of either risperidone (one trial) or haloperidol (three trials). Studies were not powered to allow for a comparison of ABILITAT and the active comparators. Efficacy was also documented in a long-term (52-week) trial of outpatients, which compared ABILITAT to haloperidol. Patients in these trials met DSM-III/IV criteria for schizophrenia or schizoaffective disorder. Three short-term, fixed-dose trials were well-controlled and powered to statistically demonstrate the efficacy of ABILITAT over placebo.

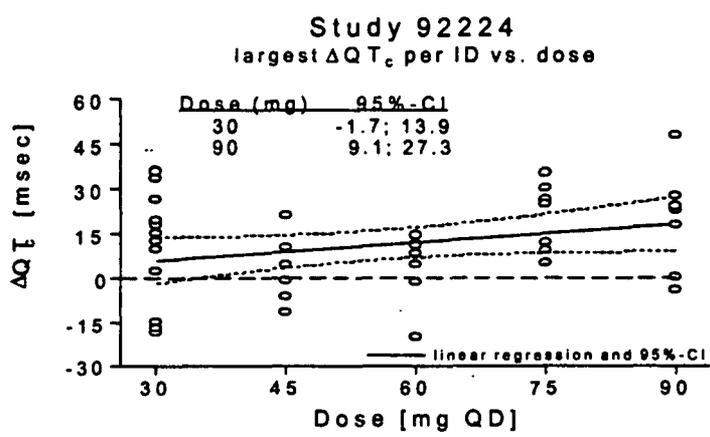
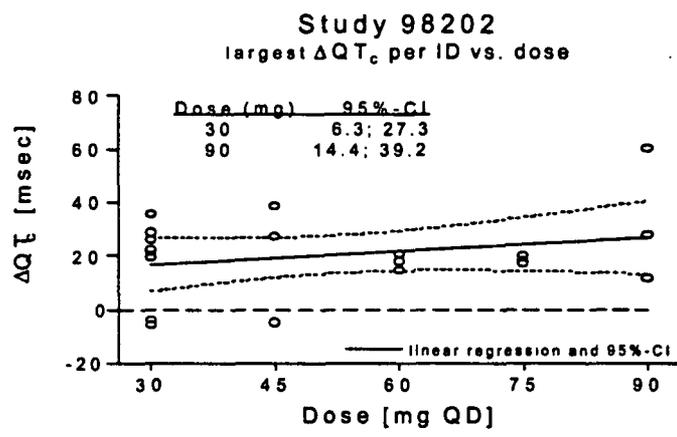
**Table 3. Key Efficacy Results in Short-Term, Placebo-Controlled Trials (Sponsor's Analyses)**

Trial Treatment	PANSS Total	PANSS Positive	PANNS Negative	PANNS-Derived BPRS	CGI Severity	CGI Improvement
	<i>Mean Change from Baseline</i>				<i>Mean Score</i>	
<b>Trial 1</b> (4-week, n=414 acutely relapsed patients, 15 or 30 mg/day A, placebo, 10 mg/day Haloperidol)						
Placebo	-2.9	-0.6	-1.2	-1.1	-0.1	4.3
A 15 mg/day	<b>-15.5**</b>	<b>-4.2**</b>	<b>-3.6**</b>	<b>-3.1**</b>	<b>-0.6**</b>	<b>3.5**</b>
A 30 mg/day	<b>-11.4**</b>	<b>-3.8**</b>	-2.3	<b>-3.0**</b>	<b>-0.4*</b>	<b>3.8*</b>
<b>Trial 2</b> (4-week, n=404 acutely relapsed patients, 20 or 30 mg/day A, placebo, 6 mg/day Risperidone)						
Placebo	-5.0	-1.8	-0.8	-1.7	-0.2	4.0
A 20 mg/day	<b>-14.5**</b>	<b>-4.9**</b>	<b>-3.4**</b>	<b>-3.5**</b>	<b>-0.5*</b>	<b>3.4**</b>
A 30 mg/day	<b>-13.9**</b>	<b>-3.9*</b>	<b>-3.4**</b>	<b>-3.3*</b>	<b>-0.6**</b>	<b>3.3**</b>
<b>Trial 3</b> (6-week, n=420 acutely relapsed patients, 10, 15, or 20 mg/day A, placebo)						
Placebo	-2.3	-1.1	-0.1	-1.4	-0.2	4.0
A 10 mg/day	<b>-15.0**</b>	<b>-5.0**</b>	<b>-3.5**</b>	<b>-3.9**</b>	<b>-0.7**</b>	<b>3.3**</b>
A 15 mg/day	<b>-11.7**</b>	<b>-3.8*</b>	<b>-2.6**</b>	<b>-2.9*</b>	<b>-0.5*</b>	<b>3.4**</b>
A 20 mg/day	<b>-14.4**</b>	<b>-4.5*</b>	<b>-3.3**</b>	<b>-3.6**</b>	<b>-0.6**</b>	<b>3.3**</b>

\*\* (P≤0.01), \* (0.01<P<0.05) significantly different from placebo. Results in bold indicate the protocol-specified primary efficacy measures.

**Safety** – The objective of the population PK/Safety analysis of aripiprazole was to assess the relationship between patients' aripiprazole plasma concentrations and QT<sub>c</sub> prolongation. The data from the Studies 31-97-201 and 31-97-202 were used for the analysis. The data included 251, 506, and 616 QT<sub>c</sub> observations from respectively 184, 313, and 328 aripiprazole patients in the 2-h, 12-h, and 48-h window (the maximum time difference between ECG and blood draw). A linear mixed-effects regression model was fitted to the data. Regardless of the heart rate correction formula and time window selected for analysis, no relationships could be determined between the change from baseline of QT<sub>C,B</sub> (Bazett), QT<sub>C,F</sub> (Fredericia) or QT<sub>C,n</sub> (fractional exponent) and the corresponding plasma concentrations of aripiprazole. The variability in changes from baseline of QT<sub>c</sub> in aripiprazole patients was comparable to that in placebo patients. The OCPB Pharmacometrics Reviewer used a population modeling approach to arrive at corrected QT values and conclusion similar to the sponsor's was made that no change in corrected QT as a function of dose or concentration could be detected.

Although in the recommended dose range (15-30 mg), QT<sub>c</sub> increase was not correlated to dose, at doses greater than 30 mg (45-90 mg/day) larger increase in QT<sub>c</sub> was observed (Pharmacometrics Reviewer provided this data analysis):





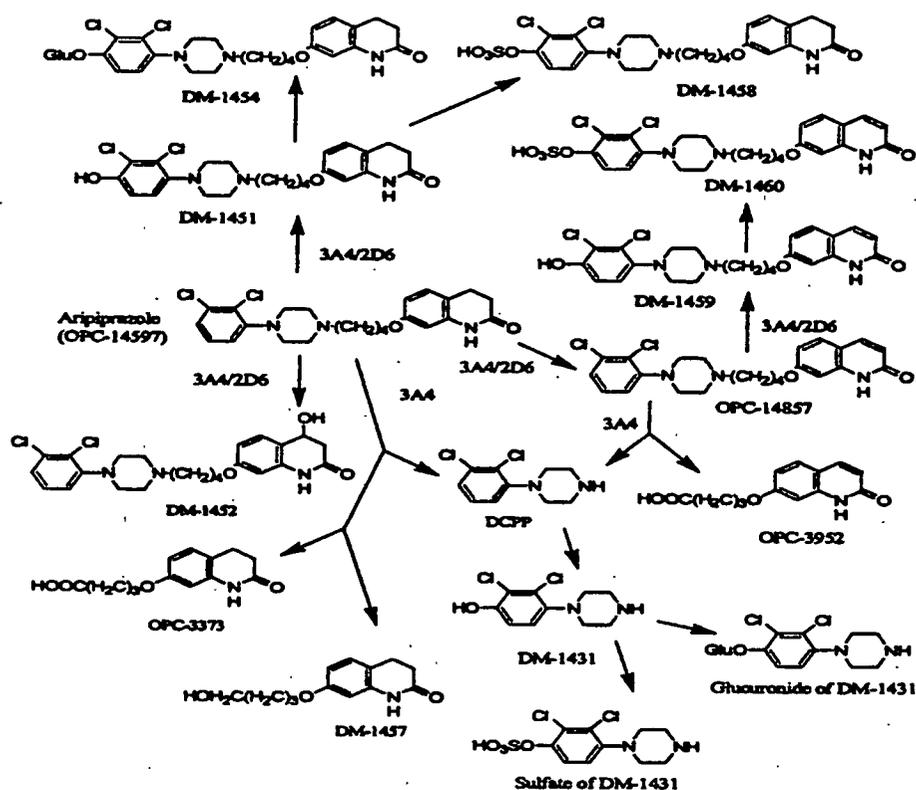
**Metabolism** The biotransformation profiles of radioactivity in plasma, urine and feces after oral administration of  $^{14}\text{C}$ -labeled aripiprazole in healthy volunteers show that aripiprazole is mainly eliminated by metabolic clearance in humans. Three biotransformation pathways identified *in vitro* and *in vivo* are: dehydrogenation, *N*-dealkylation, and hydroxylation. (1) Dehydrogenation of aripiprazole introduces a double bond in the quinolinone ring with the formation of an active metabolite OPC-14857. (2) *N*-dealkylation splits aripiprazole molecule to the quinolinone moiety with the butyl side chain (OPC-3373), and *N*-2,3-dichlorophenyl piperazine (DCPP). (3) Hydroxylation occurs either at the benzylic carbon of the quinolinone ring to form metabolite DM-1452 or in the dichlorophenyl ring to form an aromatic hydroxy metabolite, DM-1451. Some of these primary metabolites undergo subsequent biotransformation reactions, including *N*-dealkylation, hydroxylation and glucuronide and sulfate conjugations. As aripiprazole is not directly conjugated, it is not expected to have pharmacokinetic interactions with drugs eliminated via conjugation.

Aripiprazole was the predominant species in plasma (57% of the total radioactivity). OPC-14857 was the major circulating metabolite (accounting for 20% of the total radioactivity), followed by OPC-3373, the acid-product of aripiprazole *N*-dealkylation (<2% of the total radioactivity). Minor metabolites in plasma were monohydroxy metabolite DM-1451 and DM-1452, DM1454 (the glucuronide of DM-1451), DM-1458 (the sulfate of DM-1451) and DM-1459 (dehydro hydroxy aripiprazole), each of which accounted for 1 to 3% of the total radioactivity in one or more of the plasma samples.

The enzymes responsible for the three primary biotransformation pathways in humans were determined by *in vitro* metabolism studies with recombinant human cytochrome P450 isoforms and human liver microsomes. Both CYP3A4 and CYP2D6 were responsible for dehydrogenation and hydroxylation; whereas, *N*-dealkylation was catalyzed by CYP3A4. Other CYP isoforms, namely 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2E1, were not involved in the metabolism of aripiprazole. The proposed metabolic pathways are shown in next page.

**Excretion:** Aripiprazole is eliminated via metabolism. Its metabolites are eliminated by both the renal and biliary routes in humans. Less than 1% of an oral dose of aripiprazole is excreted unchanged in urine; 8%-18% was recovered unchanged in the feces. Relatively small molecular weight *N*-dealkylation derived metabolites (OPC-3373 and DCPP-related) were excreted predominantly in urine; whereas the large molecular weight hydroxy- and dehydro- metabolites were eliminated by the biliary route, most likely subsequent to conjugation with sulfate and glucuronide. The recovery of radioactivity from the urine and feces after administration of 20 mg dose of [ $^{14}\text{C}$ ]-labeled aripiprazole (Table 5) or 5 mg dual labeled [ $^{14}\text{C}$ ]-aripiprazole (Table 6) to healthy subjects (Table 6) are summarized below:

**Figure 1. Proposed Aripiprazole Metabolic Pathways**



**Table 5. Summary of Recoveries from Urine and Feces (% of Radioactive Dose, Study 96-201, N=12)**

Urine (% of total)	OPC-3373	OPC-3952	U-1	U-2			
25.52±3.98	19.2±4.07	5.18±0.91	0.82±0.50	0.33±0.18			
Feces (% of total)	Parent	OPC-14857	DM-1451	OPC-3952	U-4	U-5	U-6
55.18±6.60	18.32±10.9	3.28±1.92	14.93±5.67	14.68±5.37	0.44±0.80	4.88±2.98	0.41±0.40

Over 648-720 h

**Table 6. Relative Distribution of Radioactivity Percent among Various Peaks in the Radiochromatographic Profiles of Pooled Urine and Feces from Humans (Study 138-028)**

		Urine (0-384 h)	Feces (0-384 h)	
Total	% (N=6)	35.7±3.5	% (N=6)	43.9±18.1
OPC-3373	--	42%	DM-1451	53%
Glucuronide of DM-1431	14%		DM-1459	19%
OPC-3952	10%		OPC-14857	9%
Sulfate of DM-1431	8%		Aripiprazole	8%
DM-1431	5%		DM-1452	trace
DM-1454, DM-1457	1%, 1%		Others	8%
DCPP	trace			
Others	14%			
Total		95%	Total	97%

Gallbladder sand and/or stones were observed in monkeys after doses of 25 to 125 mg/kg/day in subchronic and chronic toxicity studies. A clinical pharmacology study has determined the concentrations of the conjugates of aripiprazole metabolites in bile after daily oral doses of 15-30 mg of aripiprazole for 7 days. It was found that the highest in vivo concentration of DM-1458, DM1454 and DM-1460 in bile across all subjects were no more than 6% of the lowest bile concentrations found in the monkeys in the 39 week study and are well below ( $\leq 6\%$ ) their limits of in vitro solubility. Therefore, it was concluded that in healthy subjects administered up to and including 30 mg aripiprazole per day these conjugates will not likely reach concentrations that result in precipitation and consequent formation of gall stones.

**Pharmacokinetics:** The terminal half-life is 75 hours (range 31-146 hours) for aripiprazole and 94 hours for its active metabolite OPC-14857. During QD administration, steady-state concentrations of aripiprazole and OPC-14857 are achieved after 2 weeks. At steady-state the  $C_{max}$  occurs at 3-5 hours post dose and the fluctuation in plasma concentrations is 40%. The steady-state accumulation index of aripiprazole is 5, in keeping with its 75 hours half-life. At steady-state, the systemic exposure of the active metabolite is 40% of the parent drug. The mean total body clearance of aripiprazole, which was primarily hepatic, was estimated to be 50 ml/h/kg, suggesting that aripiprazole is a low hepatic extraction drug in humans.

Following a single 10 mg dose of aripiprazole, CYP2D6 poor metabolizer (PM) subjects had a 41% lower clearance of aripiprazole than CYP2D6 extensive metabolizer (EM) subjects. Plasma concentrations of the active metabolite, OPC-14857, were decreased by 37% in the PM subjects relative to the EM. The sponsor claims that the magnitude of the increase for aripiprazole plasma concentrations was complementary to the magnitude of the decrease for OPC-14857. As aripiprazole and OPC-14857 have comparable affinity to the  $D_2$  receptor and display similar protein binding, the effects of CYP2D6 PM genotype are not expected to result in a change in the safety or efficacy profile of aripiprazole. Therefore no dose adjustment is routinely required based on CYP2D6 metabolism genotype or phenotype (see OCPB Comment in later section).

**Dose Proportionality and Linearity** - The dose proportionality of aripiprazole was assessed by examining the AUC,  $C_{max}$  and the oral clearance as a function of the dose (5-30 mg) from two multiple dose studies. Linear regression of oral clearance vs. dose indicated that the slope was not significantly different from zero; linear regression of the untransformed AUC and  $C_{max}$  showed that the confidence interval of the intercept included zero; and regression of the log transformed AUC and  $C_{max}$  as a function of log dose showed that the confidence interval of the slope included 1, indicating that the pharmacokinetics of aripiprazole were linear and dose-proportional across the doses studied. In schizophrenia patients, the pharmacokinetics of aripiprazole appear to be linear at doses ranging from 30-75 mg per day.

**5. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

In adult healthy volunteers with CYP2D6 EM status, moderate intersubject variability (16-57% for C<sub>max</sub> and 27-60% for AUC) and low intrasubject variability (14-18% for C<sub>max</sub> and 8-11% for AUC) were observed for aripiprazole pharmacokinetic parameters. Similar variability was observed in patient population. Pharmacokinetics of aripiprazole was studied in only 5 healthy subjects with CYP2D6 poor metabolizer status. Also, efficacy and safety of aripiprazole have not been adequately studied in CYP2D6 poor metabolizer population.

**4.3 Intrinsic Factors**

**1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?**

The results of phase I trials and population pharmacokinetic analysis (a non-linear mixed effects modeling approach) of Phase II and Phase III trials demonstrate that there is no difference in the pharmacokinetics of aripiprazole between healthy subjects and patients with schizophrenia. In addition, this population pharmacokinetic analysis found no effect of race (Caucasian, Black, Hispanic, Asian, other) or gender on the pharmacokinetics of aripiprazole. The analysis done by the OCPB Pharmacometrics Reviewer has found a 22% increase in aripiprazole clearance for smokers relative to non-smokers. No dose adjustment is routinely required based on race, gender or smoking status.

**2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups?**

**Genotype:** Aripiprazole is a substrate for CYP2D6. Approximately 7% of Caucasians have decreased capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) whereas the rest are extensive metabolizers (EM). Following a single 10 mg dose of aripiprazole, the differences in major pharmacokinetic parameters of aripiprazole in CYP2D6 poor metabolizers (PM, N=5) compared to CYP2D6 extensive metabolizers (EM, N=12) are summarized below:

**Table 7. Changes (%) in Pharmacokinetic Parameters in CYP2D6 Poor metabolizers Compared to CYP2D6 Extensive Metabolizers**

Parameter	Aripiprazole				OPC-14857		OPC-3373	
	C <sub>max</sub>	AUC <sub>∞</sub>	CL/F	t <sub>1/2</sub>	C <sub>max</sub>	AUC <sub>∞</sub>	C <sub>max</sub>	AUC <sub>t</sub>
CYP2D6 PMs (n=8)	-7%	+82%	-41%	+73%	-46%	-34%	-9%	+38%

The sponsor claims that the magnitude of the increase for aripiprazole plasma concentrations was complementary to the magnitude of the decrease for OPC-14857 and

the effect of CYP2D6 PM genotype are not expected to result in a change in the safety or efficacy profile of aripiprazole. Therefore, no dose adjustment is routinely required based on CYP2D6 metabolism genotype or phenotype. In fact, as aripiprazole and OPC-14857 have comparable affinity to the D<sub>2</sub> receptor, display similar protein binding and are equally potent, there is approximately 65% higher systemic exposure to active moieties in PM subjects. The efficacy and safety of aripiprazole have not been adequately studied in PM subjects.

**Gender:** Gender effect study revealed that C<sub>max</sub> and AUC of aripiprazole and its active metabolite OPC-14857 were 30-40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole (not normalized by body weight) was lower in women. However, these differences were largely explained by differences in body weight (25%) between men and women.

**Race:** Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation of data from 396 Caucasians, 217 Blacks, 53 Hispanics, 15 Asians, and 13 subjects of other races revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole.

**Elderly:** Age effect study revealed that aripiprazole clearance decreased by 20% in elderly (≥65 yrs) subjects compared to younger adult subjects (18-64 yrs) following a single 15 mg dose. There was no detectable effect of age in the population pharmacokinetic analysis in schizophrenic patients. In addition, the pharmacokinetics of aripiprazole during multiple dose administration to elderly patients with dementia appears similar to that observed in young healthy subjects. Therefore, no dose adjustment is recommended for elderly population.

**Pediatric Population:** Children (6-12 yrs) with conduct disorder were found to have a 34% lower steady-state oral clearance of aripiprazole than adolescents (13-17 yrs) with conduct disorder or healthy adult subjects. When oral clearance was normalized to total body weight, the values for the mean apparent oral clearance were similar across children, adolescents, and adults. The safety and effectiveness of ABILITAT for the treatment of schizophrenia in pediatric and adolescent patients has not been established.

**Hepatic Impairment:** Following a single 15 mg dose, the major pharmacokinetic changes of aripiprazole in subjects with varying degrees of hepatic impairment (mild, moderate, severe) compared to healthy subjects are summarized below:

**Table 8. Changes (%) in Pharmacokinetic Parameters in Hepatic Impairment Subjects Compared to Healthy Subjects**

Parameter	Aripiprazole				OPC-14857		OPC-3373	
	C <sub>max</sub>	AUC <sub>∞</sub>	CL/F	CL/Fu	C <sub>max</sub>	AUC <sub>∞</sub>	C <sub>max</sub>	AUC <sub>t</sub>
Mild HI (n=8)	+14%	+31%	-25%	-37%	-32%	-21%	-20%	+83%
Moderate HI (n=8)	-26%	+7%	-19%	-22%	-45%	-27%	-50%	-51%
Severe HI (n=3)	-43%	-21%	+9%	-19%	-55%	-18%	-12%	+10%

The sponsor claims that this study did not reveal a meaningful effect of hepatic impairment on the pharmacokinetics of aripiprazole, therefore, no dosage adjustment is recommended due to hepatic impairment alone.

The drug exposure is generally lower in hepatic impairment subjects compared to that in healthy subjects except for subjects with mild HI (31% and 83% increases in AUC for aripiprazole and OPC-3373, respectively). There are no clear trends as to how the degrees of HI affect aripiprazole pharmacokinetics.

The pharmacokinetic result of this study was complicated by concomitant medication. Seven subjects in the HI groups were concomitantly taking spironolactone; two of them in mild HI group had terminal elimination half-life of aripiprazole greater than 240 hours. Two subjects in moderate HI group also had longer half-life (>240 hours) without taking any concomitant medication. The sponsor claims that there does not appear to be any spironolactone-related assay interference or likelihood of enzyme inhibition that could account for the prolonged half-life. Although all subjects were classified as CYP2D6 EM genotype at entry into the study, subjects with HI were sub-classified based on whether the subjects had any mutant alleles. It was concluded that there was no consistent pattern that would link the presence of a mutant allele with a prolonged half-life.

Since the maximum decreases in aripiprazole total clearance and unbound clearance were 25% and 37%, respectively, which was observed in the mild HI group, no dosage adjustment is recommended for HI due to pharmacokinetics changes. However, 3 out of 19 subjects with hepatic impairment had ECG changes that met the criteria for potential clinically significant abnormalities: two subjects (one with mild HI and one with moderate HI) experienced QT<sub>c</sub> prolongation to 451 msec and 475 msec, respectively on Day 6 and one with mild HI suffered first degree AV block on Day 1 after the single dose of aripiprazole. Therefore, aripiprazole should be used with caution in subjects with hepatic impairment.

**Renal Impairment:** After a single 15 mg dose of aripiprazole, C<sub>max</sub> of aripiprazole and OPC-14857 increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for OPC-14857 in subjects with severe renal impairment (creatinine clearance <30 ml/min) compared to that in healthy subjects. The exposure of OPC-3373 were 26-fold higher, and the renal excretion of OPC-3373, which is predominantly excreted in urine, was 2-fold lower in subjects with severe RI compared to healthy subjects. However, the increased exposure of OPC-3373 was only 5% of aripiprazole exposure. Since less than 1% of unchanged aripiprazole and the active metabolite OPC-14857 was excreted in urine, no dose adjustment is routinely required in subjects with renal impairment.

**Pregnancy and Lactation:** No adequate and well-controlled studies have been conducted in pregnant women. The sponsor proposed labeling states ' \_\_\_\_\_

\_\_\_\_\_ . Aripiprazole should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. It is not known if aripiprazole is

excreted in human milk. The sponsor proposed labeling states:

#### 4.4 Extrinsic Factors

1. *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?*

##### **Influence of Extrinsic Factors**

**Smoking:** Population pharmacokinetic analysis performed by the sponsor found no effect of smoking status on the pharmacokinetics of aripiprazole. The analysis done by the OCPB Pharmacometrics Reviewer has found a 22% increase in aripiprazole clearance for smokers relative to non-smokers. No dose adjustment is required based on smoking status.

**Alcohol-** Blood ethanol concentrations, performance of gross motor skills and stimulus response were not significantly different between ethanol co-administered with aripiprazole on Day 14 (10 mg/day of aripiprazole was administered for 14 days) and ethanol coadministered with placebo. These findings support the lack of a pronounced interaction of aripiprazole with ethanol, however, as with most psychoactive medications caution should be observed with the combination. Patients should be advised to avoid alcohol while taking aripiprazole.

**Diurnal Variation:** After a single 20 mg dose of aripiprazole was administered orally to healthy subjects in the morning or evening,  $C_{max}$  and AUC of aripiprazole were 23% and 12% lower and  $T_{max}$  occurred about 6 hours later when administered during the evening compared to the morning. These differences were not observed for the active metabolite OPC-14857. Greater variability was observed in the AUC values (CV of 37%) of aripiprazole following AM dosing compared to PM dosing (CV of 21%); this was not observed in its  $C_{max}$ , which had similar variability for both dosing times (CV of 19%). These differences in  $C_{max}$  and  $T_{max}$  values are unlikely to be clinically significant, therefore, aripiprazole may be dosed regardless of the time of day.

**Activated Charcoal:** Activated charcoal administered one hour after a single 15 mg dose of aripiprazole to 9 healthy subjects decreased plasma aripiprazole and OPC-14857 exposures ( $C_{max}$  and AUC) by 50%, which suggests that this treatment may be effective for aripiprazole overdose.

##### **Drug-Drug Interactions**

###### ***Effects of Other Drugs on Aripiprazole***

*In vitro* studies showed that CYP3A4 and CYP2D6 were the primary isozymes responsible for aripiprazole metabolism. Clinical drug interaction studies were conducted to investigate the effect of CYP2D6 and CYP3A4 inhibitors and other concomitant drugs on aripiprazole pharmacokinetics.

**Ketoconazole** – Ketoconazole is a known potent inhibitor of CYP3A4. Following a single 15 mg dose of aripiprazole to 18 healthy subjects, the effects of ketoconazole (200 mg/day for 14 days), a potent inhibitor of CYP3A4, on major aripiprazole pharmacokinetic parameters are shown in the following table:

**Table 9. Changes (%) in Pharmacokinetic Parameters after Concomitant Aripiprazole and Ketoconazole (200 mg/day) Administration Compared to Aripiprazole Alone**

Parameter	Aripiprazole			OPC-14857			OPC-3373	
	C <sub>max</sub>	AUC <sub>∞</sub>	CL/F	C <sub>max</sub>	AUC <sub>∞</sub>	CL/F	C <sub>max</sub>	AUC <sub>t</sub>
Arip+Ketoc (n=18)	+37%	+63%	-40%	+43%	+77%	-44%	-50%	+118%

The sponsor claims that these increases in aripiprazole and its active metabolite by ketoconazole inhibition were not regarded as clinically meaningful, since aripiprazole doses of 15 to 30 mg have shown efficacy in schizophrenia and higher doses have been well tolerated by patients.

OCPB reviewer does not agree with the sponsor's conclusion. The sponsor has not studied the worst-case scenario that 400 mg/day clinical dose of ketoconazole is coadministered with aripiprazole. It is expected that there will be even higher increases in the systemic exposure of active moieties when both drugs are coadministered at clinical dose. When concomitant administration of aripiprazole and ketoconazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. The effect of ketoconazole coadministered with aripiprazole in CYP2D6 poor metabolizers has not been studied.

**Quinidine** – Quinidine is a known potent inhibitor of CYP2D6 at doses of ≥50 mg of quinidine base. Following a single 10 mg dose of aripiprazole to 12 healthy subjects with CYP2D6 EM status, the effects of quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, on aripiprazole major pharmacokinetic parameters are summarized in the following table:

**Table 10. Changes (%) in Pharmacokinetic Parameters after Concomitant Aripiprazole and Quinidine (166 mg/day) Administration Compared to Aripiprazole Alone**

Parameter	Aripiprazole			OPC-14857		OPC-3373	
	C <sub>max</sub>	AUC <sub>∞</sub>	CL/F	C <sub>max</sub>	AUC <sub>∞</sub>	C <sub>max</sub>	AUC <sub>t</sub>
Arip+Quinidine (n=12)	+13%	+112%	-52%	-46%	-34%	-16%	-23%

The systemic exposure of aripiprazole and its active metabolite OPC-14857 were similar for EM subjects coadministered quinidine with aripiprazole and for PM genotype subjects. The sponsor claims that as aripiprazole and OPC-14857 are equipotent at the D2 receptor and display similar protein binding, the net effects of CYP2D6 inhibition are not expected to result in a change in the safety or efficacy profile of aripiprazole. OCPB reviewer recommends that aripiprazole dose should be reduced at least to one-half of its normal dose when concomitant administration of aripiprazole and quinidine occurs in EM subjects (see explanation under genotyping). The effect of both potent CYP2D6 and CYP3A4 inhibitors coadministered with aripiprazole in CYP2D6 extensive metabolizers has not been studied.

**Carbamazepine** – Carbamazepine, an anti-epileptic agent which is frequently administered as a mood stabilizer, is a potent inducer of CYP3A4. In an ongoing clinical study,

Results from 3 patients are shown in the following table:

**Table 11. Changes (%) in Pharmacokinetic Parameters after Concomitant Aripiprazole and Carbamazepine (200 mg, BID) Administration Compared to Aripiprazole Alone**

Parameter	Aripiprazole				OPC-14857		
	C <sub>max</sub>	C <sub>min</sub>	AUC <sub>τ</sub>	CL/F	C <sub>max</sub>	C <sub>min</sub>	AUC <sub>τ</sub>
Arip+Carbam (n=3)	-58%	-72%	-61%	+176%	-61%	-69%	-63%

Although the data came from only three patients, coadministration of carbamazepine with aripiprazole resulted in more than 50% decrease in C<sub>max</sub>, C<sub>min</sub> and AUC values of both aripiprazole and its active metabolite OPC-14857, and nearly a 2-fold increase in aripiprazole clearance.

The sponsor claims that given aripiprazole's broad efficacious dose range this change in clearance may not have a clinically significant impact, however dose adjustments of aripiprazole should be guided by clinical judgment. With nearly a 2-fold increase in aripiprazole clearance caused by the coadministration of aripiprazole with carbamazepine, dose adjustment is warranted. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be increased, and when carbamazepine is withdrawn from combination therapy, aripiprazole dose should be reduced.

**Valproate** – Valproate is a mood stabilizer that is frequently coadministered with anti-psychotics. Coadministration of therapeutic doses of valproate (350-1500 mg/day) for 21 days to patients with schizophrenia or schizoaffective disorder with 30 mg QD aripiprazole resulted in the following changes in aripiprazole pharmacokinetics:

**Table 12. Changes (%) in Pharmacokinetic Parameters after Concomitant Aripiprazole and Valproate Sodium (350-1500 mg/day) Administration Compared to Aripiprazole Alone**

Parameter	Aripiprazole				OPC-14857		
	C <sub>max</sub>	C <sub>min</sub>	AUC <sub>τ</sub>	CL/F	C <sub>max</sub>	C <sub>min</sub>	AUC <sub>τ</sub>
Arip+Valproate (n=6)	-26%	-22%	-24%	+32%	-7%	-11%	-8%

Valproate is a broad-spectrum inhibitor of UGT enzymes, epoxide hydrolase, and CYP2C9 enzymes. There is no data suggesting that valproate is an inhibitor of CYP2D6 enzyme or an inducer of CYP3A4 and /or CYP2D6. This increase in the oral clearance of aripiprazole in the presence of divalproex sodium is not likely due to enzymatic induction since aripiprazole's major metabolic pathway are mediated by CYP3A4 and CYP2D6. As valproate and aripiprazole share the same plasma protein binding site II, valproate is likely to act as a protein displacer when coadministered with aripiprazole, and the decrease in the aripiprazole steady-state concentration and AUC values is consistent with this hypothesis. The magnitude of decrease in aripiprazole exposure caused by coadministration with valproate is not considered clinically important, therefore, dose adjustment is not required.

**Lithium** - Lithium is a mood stabilizer that is frequently coadministered with anti-psychotics. Coadministration of therapeutic doses of lithium (1200-1800 mg/day) for 21 days to patients with schizophrenia or schizoaffective disorder with 30 mg QD aripiprazole had no clinically significant effect on the pharmacokinetics of aripiprazole or OPC-14857 ( $C_{max}$  and AUC increased by less than 20%). Because lithium is not bound to plasma proteins, is not metabolized, and is excreted almost entirely in the urine in humans no effects on lithium pharmacokinetics are expected with aripiprazole. No dose adjustment is required with lithium coadministration.

The sponsor claims that there was no evidence of EEG findings suggestive of epileptiform activity, encephalopathy, or other pathological EEG rhythms with the coadministration of lithium, valproate or carbamazepine with aripiprazole supporting the safety of these combinations.

**Population Pharmacokinetic Analysis** - The sponsor conducted a population pharmacokinetic analysis using the data from 5 Phase II and Phase III studies, and concomitant medications were tested as possible covariates in the population pharmacokinetic model to assess their effects on aripiprazole pharmacokinetics. Drugs from the following groups were examined: substrates and inhibitors of CYP3A4, substrates and inhibitors of CYP2D6, drugs that raise gastric pH, substances of abuse and benzodiazepines. Several drugs were also considered separately as covariates, including lorazepam, ketoconazole, haloperidol, ranitidine, combination antacids and adsorbents, magnesium hydroxide, famotidine, omeprazole, clonazepam and temazepam. Although the analysis indicated no dosage adjustment for aripiprazole is needed when it is coadministered with any of the medications, the number of patients on the individual concomitant medications, except benzodiazepines, was too small to be conclusive.

#### **Effects of Aripiprazole on Other Drugs**

Based on the high ratio of the *in vitro*  $IC_{50}$ s to unbound maximum plasma concentrations of aripiprazole and its metabolite OPC-14857 (>1196), aripiprazole is not expected to significantly inhibit the *in vivo* activity of CYP1A2, 2C9, 2C19, 2D6, and 3A4 at clinically relevant plasma concentrations. A series of drug interaction studies with various marker CYP substrates were conducted to investigate the potential of aripiprazole on the metabolism of other drugs.

**Dextromethorphan** - It was found that doses of 10 and 30 mg per day of aripiprazole for 14 days in CYP2D6 extensive metabolizers had no effects on dextromethorphan O-dealkylation, a pathway known to be dependent on CYP2D6 activity (DM/DRP ratio was 0.03 both with and without coadministered aripiprazole). Aripiprazole 30 mg QD for 14 days also had no effect on dextromethorphan N-demethylation, a pathway known to be dependent on CYP3A4 (the ratio of the  $A_e$  of DM to its metabolite 3-methoxymorphan [MMP] has been used to assess CYP3A4 activity).

**Warfarin** - Aripiprazole 10 mg QD for 14 days had no effect on the pharmacokinetics of R or S warfarin (CYP2C9 substrate) in healthy subjects. In addition, there was no effect

of aripiprazole on the International Normalized Ratio, indicating the absence of a pharmacodynamic interaction and no perturbation of warfarin protein binding.

**Omeprazole** – It was found that in healthy subjects there was no effect of 10 mg QD aripiprazole on the pharmacokinetics of omeprazole, a recognized substrate for CYP2C19.

The results of these studies confirmed that aripiprazole has low potential to affect the pharmacokinetics of medications metabolized by CYP1A2, 2C9, 2C19, 2D6, and 3A4.

#### 4.5 General Biopharmaceutics

1. *Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?*

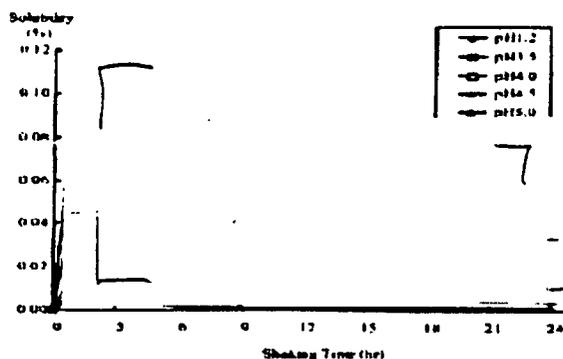
**Solubility** - Aripiprazole is practically insoluble in water. However, it is a base, with pKa of 7.6 and has a pH-dependent solubility profile:

**Table 13. pH-Solubility Profile of Aripiprazole at 25°C**

Buffer pH	pH after Equilibration	Solubility (mg/ml)
2.0	3.2	-
3.0	3.5	
4.0	4.1	
5.0	5.0	
6.0	6.0	
7.0	7.0	
8.0-12.0	8.0-12.0	
Water	--	--

Equilibration by shaking for 72 hours, then allowing to stand for 24 hours. Solubility cut-off 30mg/250ml=0.12 mg/ml.

**Figure 2. pH-Solubility Profile in USP HCl Buffer (pH 1.2) and Acetate Buffer (pH 3.5-pH 5) at 37°C**



The solubility and dissolution rate of aripiprazole from pH 5.0 to 2.0. However, below pH 2.0, a decrease in dissolution rate was observed. It was confirmed that the formation of aripiprazole-HCl salt at low pH and reduction in its solubility due to common ion effect are responsible for slower dissolution.